Michael D. Gershon, M.D.
Professor and Chair
Department of Anatomy & Cell Biology
Columbia University, P&S
630 West 168th Street
New York, NY 10032

Janet Woodcock, M.D.
Director, CDER
c/o Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Park Lawn Drive
Rockville, MD

Dear Dr. Woodcock,

I write to urge you to carefully consider the preponderance of evidence that has clearly demonstrated that alosetron provides a safe and effective treatment for female patients with diarrhea-predominant irritable bowel syndrome (IBS).

I apologize for sending my concerns to you by fax, but I am out of the country right now and I do not have access to a typewriter or printer. Please forgive me for this unorthodox, if modern, means of communication.

I understand that alosetron is under attack by Sydney Wolfe and his group, "Public Citizen". I have seen Dr. Wolfe's letter to you, which demands that alosetron be withdrawn from the market. In his intemperate letter, Dr. Wolfe makes many claims, none of which are supported by real evidence. Among the most egregious of these defective claims, is his implication that alosetron causes ischemic colitis. To be sure, ischemic colitis has occurred in individuals who have taken alosetron; however, that coincidence does not, by itself, establish that the patients developed ischemic colitis because they took alosetron.

Clearly, to show that alosetron causes ischemic colitis, or even increases the likelihood of contracting it, one would have to show, as a minimum, that the incidence of ischemic colitis is higher in people who take alosetron than it is in people who do not take alosetron. Even then, one would want to know whether additional factors might also

be operative. Dr. Wolfe, however, does not even consider the background incidence of ischemic colitis. His polemic, which fails to mention that ischemic colitis does occur in people for reasons unrelated to the ingestion of alosetron, argues as if he were unaware that the underlying incidence of ischemic colitis might be relevant.

The actual incidence of ischemic colitis is not precisely known, but a very large survey of patients with gastrointestinal disease has been carried out and has been cited by GlaxoWellcome. This survey suggests that the incidence of ischemic colitis in patients who have taken alosetron (about 1/900) is not significantly higher than that which prevails in the general population (about 1/800). Dr. Wolfe cites raw reports of untoward events that must be analyzed before they can be known to be relevant to the use of alosetron. How much alosetron these patients consumed and when they consumed it in relation to when ischemic colitis occurred are, for example important factors that do not appear in the raw reports.

Additional flaws in Dr. Wolfe's argument are his attempts to denigrate the severity of IBS and the efficacy of alosetron in its treatment. IBS is, for many of the individuals it affects, a terrible condition that has the ability to virtually destroy the quality of life. The disease occurs most commonly in women. The impact of IBS is often trivialized by sexist and uncaring males who consider it to be a psychosomatic manifestation of the hysterical nature of women. Nothing in the literature provides any support at all for this misguided view, which seems very much to be that of Dr. Wolfe. In fact, modern evidence is consistent with the idea that IBS is, as its symptoms suggest, a primary disease of the gut. Alosetron has been demonstrated to be efficacious in the treatment of diarrhea-predominant IBS, and nothing Dr. Wolfe alleges changes that. An advisory panel of the FDA has reviewed the evidence and accepted it. The data are real and they stand unchallenged. Alosetron is as effective for the treatment of IBS as NSAIDS are for the treatment of arthritis.

Clearly, the rules of evidence cannot be repealed because of the personal revulsion Dr. Wolfe apparently feels for corporations and the compounds they produce. It would be unfair to millions of women with IBS who need alosetron for the FDA to bow to his political pressure and interfere with the opportunity of these women to gain relief from IBS through alosetron's use.

In summary, I would hope that you and the FDA realize that correlation does not establish causation and that simple coincidence does not even establish correlation. Dr. Wolfe has yet to show that anything more serious than that a small number of coincidences of ischemic colitis and alosetron use have occurred. Whether or not

something else might have transpired in the patients that were cited by Dr. Wolfe who experienced ischemic colitis that might have led to them to get the problem was not something he considered. Several hundred years before the common era, in Ionia (the Aegean coast of what is now Turkey), Thales introduced the philosophy of rationalism. His concept, still accepted by science, was to assume causality; that is, for every event there must be a natural cause that can be understood by the human mind. Hopefully, the FDA will not now abandon the principles of rationalism. Alosetron should continue to be used and patients who need alosetron should not be irrationally discouraged from using it.

Thank you for considering my views.

Sincerely yours,

Michael D. Gershon, M.D.
Tel: 212-305-3447
Fax: 212-305-3970
Email: mdg4@columbia.edu